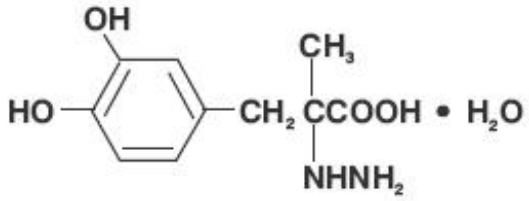
CARBIDOPA AND LEVODOPA- carbidopa and levodopa tablet, extended release
NCS HealthCare of KY, Inc dba Vangard Labs

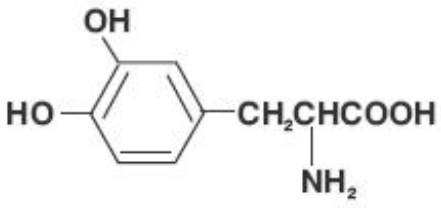
Carbidopa and Levodopa Extended-release Tablets

DESCRIPTION

Carbidopa and levodopa extended-release tablets are extended-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.
Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (-)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its molecular formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$ and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa, which has a molecular weight of 226.3. Levodopa, an aromatic amino acid, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (-)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its molecular formula is $C_9H_{11}NO_4$ and its structural formula is:



Carbidopa and levodopa extended-release tablets are supplied as extended-release tablets containing either 50 mg of carbidopa USP and 200 mg of levodopa USP, or 25 mg of carbidopa USP and 100 mg of levodopa USP. Inactive ingredients: microcrystalline cellulose, colloidal silicon dioxide, hypromellose, hydroxypropyl cellulose, magnesium stearate, red ferric oxide and D&C Yellow 10 Aluminum lake.

The 50 mg/200 mg tablet is supplied as an oval, scored, biconvex, compressed tablet debossed “457” on one side and scored on other side that is buff colored with mottled appearance. The 25 mg/100 mg tablet is supplied as an oval, biconvex, compressed tablet debossed “461” on one side and plain on other side that is buff colored with mottled appearance. Carbidopa and levodopa extended-release tablet is a polymeric-based drug delivery system that controls the release of carbidopa and levodopa as it slowly

erodes. Carbidopa and levodopa extended-release tablet 25 mg/100 mg is available to facilitate titration when 100 mg steps are required.

CLINICAL PHARMACOLOGY

Mechanism of Action

Parkinson's disease is a progressive, neurodegenerative disorder of the extrapyramidal nervous system affecting the mobility and control of the skeletal muscular system. Its characteristic features include resting tremor, rigidity, and bradykinetic movements. Symptomatic treatments, such as levodopa therapies, may permit the patient better mobility.
Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

Pharmacodynamics

When levodopa is administered orally, it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect, and these may often be accompanied by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.
Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.
Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.
Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.
Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations (`on-off' phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, in some patients they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Carbidopa and levodopa extended-release tablet contains either 50 mg of carbidopa and 200 mg of levodopa, or 25 mg of carbidopa and 100 mg of levodopa in an extended-release dosage form designed to release these ingredients over a 4- to 6-hour period. With carbidopa and levodopa extended-release tablets there is less variation in plasma levodopa levels than with carbidopa and levodopa tablets, the conventional formulation. *However, carbidopa and levodopa extended-release tablets are less systemically bioavailable than carbidopa and levodopa tablets and may require increased daily doses to achieve the same level of symptomatic relief as provided by carbidopa and levodopa tablets.*

In clinical trials, patients with moderate to severe motor fluctuations who received carbidopa and levodopa extended-release tablets *did not experience quantitatively significant reductions* in `off' time when compared to carbidopa and levodopa tablets. However, global ratings of improvement as assessed by both patient and physician were better during therapy with carbidopa and levodopa extended-release tablets than with carbidopa and levodopa tablets. In patients without motor fluctuations, carbidopa and levodopa extended-release tablets, under controlled conditions, provided the same therapeutic benefit with less frequent dosing when compared to carbidopa and levodopa tablets.

Pharmacokinetics

Carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.
Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following carbidopa and levodopa extended-release tablets, the apparent half-life of levodopa may be prolonged because of continuous absorption.
In healthy elderly subjects (56 to 67 years old) the mean time-to-peak concentration of levodopa after a single dose of carbidopa and levodopa extended-release tablets 50 mg/200 mg was about 2 hours as compared to 0.5 hours after standard carbidopa and levodopa tablets. The maximum concentration of levodopa after a single dose of carbidopa and levodopa extended-release tablets was about 35% of the standard carbidopa and levodopa tablets (1,151 vs. 3,256 ng/mL). The extent of availability of levodopa from carbidopa and levodopa extended-release tablets was about 70 to 75% relative to intravenous levodopa or standard carbidopa and levodopa tablets in the elderly. The absolute bioavailability of levodopa from carbidopa and levodopa extended-release tablets (relative to I.V.) in young subjects was shown to be only about 44%. The extent of availability and the peak concentrations of levodopa were comparable in the elderly after a single dose and at steady state after t.i.d. administration of carbidopa and levodopa extended-release tablets 50 mg/200 mg. In elderly subjects, the average trough levels of levodopa at steady state after the extended-release tablet were about 2 fold higher than after the standard carbidopa and levodopa tablets (163 vs. 74 ng/mL).
In these studies, using similar total daily doses of levodopa, plasma levodopa concentrations with carbidopa and levodopa extended-release tablets fluctuated in a narrower range than with carbidopa and levodopa tablets. Because the bioavailability of levodopa from carbidopa and levodopa extended-release tablets relative to carbidopa and levodopa tablets is approximately 70 to 75%, the daily dosage of levodopa necessary to produce a given clinical response with the extended-release formulation will usually be higher.
The extent of availability and peak concentrations of levodopa after a single dose of carbidopa and levodopa extended-release tablets 50 mg/200 mg increased by about 50% and 25%, respectively, when administered with food.

At steady state, the bioavailability of carbidopa from carbidopa and levodopa tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa. At steady state, carbidopa bioavailability from carbidopa and levodopa extended-release tablets 50 mg/200 mg is approximately 58% relative to that from carbidopa and levodopa tablets.

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

Special Populations

Geriatric: A study in eight young healthy subjects (21 to 22 yr) and eight elderly healthy subjects (69 to 76 yr) showed that the absolute bioavailability of levodopa was similar between young and elderly subjects following oral administration of levodopa and carbidopa. However, the systemic exposure (AUC) of levodopa was increased by 55% in elderly subjects compared to young subjects. Based on another study in forty patients with Parkinson's disease, there was a correlation between age of patients and the increase of AUC of levodopa following administration of levodopa and an inhibitor of peripheral dopa decarboxylase. AUC of levodopa was increased by 28% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr). Additionally, mean value of C_{max} for levodopa was increased by 24% in elderly patients (≥ 65 yr) compared to young patients (< 65 yr) (see PRECAUTIONS, *Geriatric Use*).

The AUC of carbidopa was increased in elderly subjects (n=10, 65 to 76 yr) by 29% compared to young subjects (n=24, 23 to 64 yr) following IV administration of 50 mg levodopa with carbidopa (50 mg). This increase is not considered a clinically significant impact.

INDICATIONS AND USAGE

Carbidopa and levodopa extended-release tablets are indicated in the treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

CONTRAINDICATIONS

Nonselective monoamine oxidase (MAO) inhibitors are contraindicated for use with carbidopa and levodopa extended-release tablets. These inhibitors must be discontinued at least two weeks prior to initiating therapy with carbidopa and levodopa extended-release tablets. Carbidopa and levodopa extended-release tablets may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl) (See PRECAUTIONS, Drug Interactions).

Carbidopa and levodopa extended-release tablets are contraindicated in patients with known hypersensitivity to any component of this drug, and in patients with narrow-angle glaucoma.

WARNINGS

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least twelve hours before carbidopa and levodopa extended-release tablets are started. In order to reduce adverse reactions, it is necessary to individualize therapy.
See DOSAGE AND ADMINISTRATION section before initiating therapy.

Carbidopa and levodopa extended-release tablets should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).
Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse central nervous system (CNS) effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with carbidopa and levodopa extended-release tablets than with levodopa alone.
Patients receiving carbidopa and levodopa extended-release tablets may develop increased dyskinesias compared to carbidopa and levodopa tablets. Dyskinesias are a common side effect of carbidopa and levodopa treatment. The occurrence of dyskinesias may require dosage reduction.
All patients should be observed carefully for the development of depression with concomitant suicidal tendencies.
Carbidopa and levodopa extended-release tablets should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.
As with levodopa, care should be exercised in administering carbidopa and levodopa extended-release tablets to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.
As with levodopa, treatment with carbidopa and levodopa extended-release tablets may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

Falling Asleep During Activities of Daily Living and Somnolence

Patients taking carbidopa and levodopa extended-release tablets alone or with other dopaminergic drugs have reported suddenly falling asleep without prior warning of sleepiness while engaged in activities

of daily living (includes operation of motor vehicles). Road traffic accidents attributed to sudden sleep onset have been reported. Although many patients reported somnolence while on dopaminergic medications, there have been reports of road traffic accidents attributed to sudden onset of sleep in which the patient did not perceive any warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Sudden onset of sleep has been reported to occur as long as one year after the initiation of treatment.

Falling asleep while engaged in activities of daily living usually occurs in patients experiencing preexisting somnolence, although some patients may not give such a history. For this reason, prescribers should reassess patients for drowsiness or sleepiness especially since some of the events occur well after the start of treatment. Prescribers should be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised to exercise caution while driving or operating machines during treatment with carbidopa and levodopa extended-release tablets. Patients who have already experienced somnolence or an episode of sudden sleep onset should not participate in these activities during treatment with carbidopa and levodopa extended-release tablets.

Before initiating treatment with carbidopa and levodopa extended-release tablets, advise patients about the potential to develop drowsiness and ask specifically about factors that may increase the risk for somnolence with carbidopa and levodopa extended-release tablets such as the use of concomitant sedating medications and the presence of sleep disorders. Consider discontinuing carbidopa and levodopa extended-release tablets in patients who report significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.). If treatment with carbidopa and levodopa extended-release tablets continues, patients should be advised not to drive and to avoid other potentially dangerous activities that might result in harm if the patients become somnolent. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Hyperpyrexia and Confusion

Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported in association with dose reductions or withdrawal of certain antiparkinsonian agents such as levodopa, carbidopa levodopa and carbidopa levodopa extended release. Therefore, patients should be observed carefully when the dosage of levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia. Neurological findings, including muscle rigidity, involuntary movements, altered consciousness, mental status changes; other disturbances, such as autonomic dysfunction, tachycardia, tachypnea, sweating, hyper- or hypotension; laboratory findings, such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin have been reported.

The early diagnosis of this condition is important for the appropriate management of these patients. Considering NMS as a possible diagnosis and ruling out other acute illnesses (e.g., pneumonia, systemic infection, etc.) is essential. This may be especially complex if the clinical presentation includes both serious medical illness and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology. The management of NMS should include: 1) intensive symptomatic treatment and medical monitoring and 2) treatment of any concomitant serious medical problems for which specific treatments are available. Dopamine agonists, such as bromocriptine, and muscle relaxants, such as dantrolene, are often used in the treatment of NMS; however, their effectiveness has not been demonstrated in controlled studies.

PRECAUTIONS

General

As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.
Patients with chronic wide-angle glaucoma may be treated cautiously with carbidopa and levodopa extended-release tablets provided the intraocular pressure is well-controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Dyskinesia

Levodopa alone, as well as carbidopa and levodopa extended-release tablets, are associated with dyskinesias. The occurrence of dyskinesias may require dosage reduction.

Hallucinations / Psychotic-Like Behavior

Hallucinations and psychotic-like behavior have been reported with dopaminergic medications. In general, hallucinations present shortly after the initiation of therapy and may be responsive to dose reduction in levodopa. Hallucinations may be accompanied by confusion and to a lesser extent sleep disorder (insomnia) and excessive dreaming.
Carbidopa and levodopa extended-release tablets may have similar effects on thinking and behavior. This abnormal thinking and behavior may present with one or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.
Ordinarily, patients with a major psychotic disorder should not be treated with carbidopa and levodopa extended-release tablets, because of the risk of exacerbating psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson's disease and may decrease the effectiveness of carbidopa and levodopa extended-release tablets.

Impulse Control / Compulsive Behaviors

Reports of patients taking dopaminergic medications (medications that increase central dopaminergic tone), suggest that patients may experience an intense urge to gamble, increased sexual urges, intense urges to spend money, binge eating, and/or other intense urges, and the inability to control these urges. In some cases, although not all, these urges were reported to have stopped when the dose was reduced or the medication was discontinued. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to specifically ask patients or the caregivers about the development of new or increased gambling urges, sexual urges, uncontrolled spending or other urges while being treated with carbidopa and levodopa extended-release tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking carbidopa and levodopa extended-release tablets [see Information for Patients].

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear. For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using carbidopa and levodopa extended-release tablets for any indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

Information for Patients

The patient should be informed that carbidopa and levodopa extended-release tablet is an extended-release formulation of carbidopa and levodopa which releases these ingredients over a 4- to 6-hour period. It is important that carbidopa and levodopa extended-release tablets be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the

prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa and levodopa preparations, without first consulting the physician.
If abnormal involuntary movements appear or get worse during treatment with carbidopa and levodopa extended-release tablets, the physician should be notified, as dosage adjustment may be necessary.
Patients should be advised that sometimes the onset of effect of the first morning dose of carbidopa and levodopa extended-release tablets may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of carbidopa and levodopa tablets. The physician should be notified if such delayed responses pose a problem in treatment.
Patients should be advised that, occasionally, dark color (red, brown, or black) may appear in saliva, urine, or sweat after ingestion of carbidopa and levodopa extended-release tablets. Although the color appears to be clinically insignificant, garments may become discolored.
The patient should be informed that a change in diet to foods that are high in protein may delay the absorption of levodopa and may reduce the amount taken up in the circulation. Excessive acidity also delays stomach emptying, thus delaying the absorption of levodopa. Iron salts (such as in multivitamin tablets) may also reduce the amount of levodopa available to the body. The above factors may reduce the clinical effectiveness of the levodopa or carbidopa and levodopa therapy.
Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.
Patients should be alerted to the possibility of sudden onset of sleep during daily activities, in some cases without awareness or warning signs, when they are taking dopaminergic agents, including levodopa. Patients should be advised to exercise caution while driving or operating machinery and that if they have experienced somnolence and/or sudden sleep onset, they must refrain from these activities. (See WARNINGS, Falling Asleep During Activities of Daily Living and Somnolence)
There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone and that are generally used for the treatment of Parkinson's disease, including carbidopa and levodopa extended-release tablets. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with carbidopa and levodopa extended-release tablets. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking carbidopa and levodopa extended-release tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking carbidopa and levodopa extended-release tablets. (See PRECAUTIONS, Impulse Control / Compulsive Behaviors)

Laboratory Tests

Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN) and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa and levodopa preparations than with levodopa.
Carbidopa and levodopa preparations, such as carbidopa and levodopa tablets and carbidopa and levodopa extended-release tablets, may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.
Cases of falsely diagnosed pheochromocytoma in patients on carbidopa and levodopa therapy have been reported very rarely. Caution should be exercised when interpreting the plasma and urine levels of catecholamines and their metabolites in patients on levodopa or carbidopa and levodopa therapy.

Drug Interactions

Caution should be exercised when the following drugs are administered concomitantly with carbidopa and levodopa extended-release tablets.
Symptomatic postural hypotension has occurred when carbidopa and levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with carbidopa and levodopa extended-release tablets is started, dosage adjustment of the antihypertensive drug may be required.
For patients receiving MAO inhibitors (Type A or B), see CONTRAINDICATIONS. Concomitant therapy with selegiline and carbidopa and levodopa may be associated with severe orthostatic hypotension not attributable to carbidopa and levodopa alone (see CONTRAINDICATIONS).
There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa and levodopa preparations.
Dopamine D_2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone) and isoniazid may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with carbidopa and levodopa extended-release tablets should be carefully observed for loss of therapeutic response.
Use of carbidopa and levodopa extended-release tablets with dopamine-depleting agents (e.g., reserpine and tetrabenazine) or other drugs known to deplete monoamine stores is not recommended.
Carbidopa and levodopa extended-release tablets iron salts or multivitamins containing iron salts should be coadministered with caution. Iron salts can form chelates with levodopa and carbidopa and consequently reduce the bioavailability of carbidopa and levodopa.
Although metoclopramide may increase the bioavailability of levodopa by increasing gastric emptying, metoclopramide may also adversely affect disease control by its dopamine receptor antagonistic properties.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year bioassay of carbidopa and levodopa tablets, no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 carbidopa and levodopa extended-release tablets).
In reproduction studies with carbidopa and levodopa tablets, no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 carbidopa and levodopa extended-release tablets).

Pregnancy

Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of carbidopa and levodopa tablets. There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. Carbidopa and levodopa tablets caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.
There are no adequate or well-controlled studies in pregnant women. It has been reported from individual cases that levodopa crosses the human placental barrier, enters the fetus, and is metabolized. Carbidopa concentrations in fetal tissue appeared to be minimal. Use of carbidopa and levodopa extended-release tablets in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers

Levodopa has been detected in human milk. Caution should be exercised when carbidopa and levodopa extended-release tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of the drug in patients below the age of 18 is not recommended.

Geriatric Use

In the clinical efficacy trials for carbidopa and levodopa tablets, almost half of the patients were older than 65, but few were older than 75. No overall meaningful differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals to adverse drug reactions such as hallucinations cannot be ruled out. There is no specific dosing recommendation based upon clinical pharmacology data as carbidopa and levodopa tablets and carbidopa and levodopa extended-release tablets are titrated as tolerated for clinical effect.

ADVERSE REACTIONS

In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on carbidopa and levodopa tablets were randomized to therapy with either carbidopa and levodopa tablets or carbidopa and levodopa extended-release tablets. The adverse experience frequency profile of carbidopa and levodopa extended-release tablets did not differ substantially from that of carbidopa and levodopa tablets, as shown in Table 1.

Table 1. Clinical Adverse Experiences Occurring in 1% or Greater of Patients

	Carbidopa and levodopa extended-release tablets	**Carbidopa and levodopa tablets**
	n = 491	**n = 524**
Adverse Experience	**%**	**%**
Dyskinesia	16.5	12.2
Nausea	5.5	5.7
Hallucinations	3.9	3.2
Confusion	3.7	2.3
Dizziness	2.9	2.3
Depression	2.2	1.3
Urinary tract infection	2.2	2.3
Headache	2	1.9
Dream abnormalities	1.8	0.8
Dystonia	1.8	0.8
Vomiting	1.8	1.9
Upper respiratory infection	1.8	1
Dyspnea	1.6	0.4
`On-Off' phenomena	1.6	1.1
Back pain	1.6	0.6

Dry mouth	1.4	1.1
Anorexia	1.2	1.1
Diarrhea	1.2	0.6
Insomnia	1.2	1
Orthostatic hypotension	1	1.1
Shoulder pain	1	0.6
Chest pain	1	0.8
Muscle cramps	0.8	1
Paresthesia	0.8	1.1
Urinary frequency	0.8	1.1
Dyspepsia	0.6	1.1
Constipation	0.2	1.5

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received carbidopa and levodopa extended-release tablets and 475 who received carbidopa and levodopa tablets during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.
The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with carbidopa and levodopa extended-release tablets, listed by body system in order of decreasing frequency, include:

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Cardiovascular: Palpitation, hypertension, hypotension, myocardial infarction.

Gastrointestinal: Gastrointestinal pain, dysphagia, heartburn.

Metabolic: Weight loss.

Musculoskeletal: Leg pain.

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Respiratory: Cough, pharyngeal pain, common cold.

Skin: Rash.

Special Senses: Blurred vision.

Urogenital: Urinary incontinence.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

The following adverse experiences have been reported in postmarketing experience with carbidopa and levodopa extended-release tablets:
Cardiovascular: Cardiac irregularities, syncope

Gastrointestinal: Taste alterations, dark saliva.

Hypersensitivity: Angioedema, urticaria, pruritus, bullous lesions (including pemphigus-like reactions).
Nervous System/Psychiatric: Increased tremor, peripheral neuropathy, psychotic episodes including delusions and paranoid ideation, pathological gambling, increased libido including hypersexuality, impulse control symptoms.
Skin: Alopecia, flushing, dark sweat.
Urogenital: Dark urine.
Other adverse reactions that have been reported with levodopa alone and with various carbidopa and levodopa formulations and may occur with carbidopa and levodopa extended-release tablets are:
Cardiovascular: Phlebitis.
Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.
Hematologic: Hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.
Hypersensitivity: Henoch-Schönlein purpura.
Metabolic: Weight gain, edema.
Nervous System/Psychiatric: Ataxia, depression with suicidal tendencies, dementia, euphoria, convulsions (however, a causal relationship has not been established); bradykinetic episodes, numbness, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage; consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome, nightmares.

Skin: Malignant melanoma (see also CONTRAINDICATIONS), increased sweating.

Special Senses: Oculogyric crisis, mydriasis, diplopia.

Urogenital: Urinary retention, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), bilirubin, Coombs test, uric acid.

OVERDOSAGE

Management of acute overdosage with carbidopa and levodopa extended-release tablets is the same as with levodopa. Pyridoxine is not effective in reversing the actions of carbidopa and levodopa extended-release tablets.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as carbidopa and levodopa extended-release tablets should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1,500 to 2,000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3,360 mg/kg.

DOSAGE AND ADMINISTRATION

Carbidopa and levodopa extended-release tablet contains carbidopa and levodopa in a 1:4 ratio as either the 50 mg/200 mg tablet or the 25 mg/100 mg tablet. The daily dosage of carbidopa and levodopa extended-release tablets must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. Carbidopa and levodopa extended-release tablets should not be chewed or crushed.
Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while carbidopa and levodopa extended-release tablet is being administered, although their dosage may have to be adjusted.
Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, carbidopa and levodopa extended-release tablets can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage

Patients currently treated with conventional carbidopa and levodopa preparations:
Studies show that peripheral dopa-decarboxylase is saturated by the bioavailable carbidopa at doses of 70 mg a day and greater. Because the bioavailabilities of carbidopa and levodopa in carbidopa and levodopa tablets and carbidopa and levodopa extended-release tablets are different, appropriate adjustments should be made, as shown in Table 2.

Table 2. Approximate Bioavailabilities at Steady State*

Tablet	Amount of Levodopa (mg) in Each Tablet	Approximate Bioavailability	Approximate Amount of Bioavailable Levodopa (mg) in Each Tablet
Carbidopa and levodopa extended-release tablets 50 mg/200 mg	200	0.7 to 0.75†	140 to 150
Carbidopa and levodopa tablets 25 mg/100 mg	100	0.99‡	99

* This table is only a guide to bioavailabilities since other factors such as food, drugs, and inter-patient variabilities may affect the bioavailability of carbidopa and levodopa.

† The extent of availability of levodopa from carbidopa and levodopa extended-release tablets was about 70 to 75% relative to intravenous levodopa or standard carbidopa and levodopa tablets in the elderly.

‡ The extent of availability of levodopa from carbidopa and levodopa tablets was 99% relative to intravenous levodopa in the healthy elderly.

Dosage with carbidopa and levodopa extended-release tablets should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see *DOSAGE AND ADMINISTRATION, Titration with carbidopa and levodopa extended-release tablets*). The interval between doses of carbidopa and levodopa extended-release tablets should be 4 to 8 hours during the

waking day. (See *CLINICAL PHARMACOLOGY, Pharmacodynamics.*)
A guideline for initiation of carbidopa and levodopa extended-release tablets is shown in Table 3.

Table 3. Guidelines for Initial Conversion from Carbidopa and Levodopa Tablets to Carbidopa and Levodopa Extended-Release Tablets

Carbidopa and levodopa tablets	Carbidopa and levodopa extended-release tablets
Total Daily Dose* Levodopa (mg)	Suggested Dosage Regimen
300 to 400	200 mg b.i.d.
500 to 600	300 mg b.i.d. or 200 mg t.i.d.
700 to 800	A total of 800 mg in 3 or more divided doses (e.g., 300 mg a.m., 300 mg early p.m., and 200 mg later p.m.)
900 to 1,000	A total of 1,000 mg in 3 or more divided doses (e.g., 400 mg a.m., 400 mg early p.m., and 200 mg later p.m.)

* For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, Initial Dosage-Patients currently treated with conventional carbidopa and levodopa preparations.

Patients currently treated with levodopa without a decarboxylase inhibitor:
Levodopa must be discontinued at least twelve hours before therapy with carbidopa and levodopa extended-release tablets is started. Carbidopa and levodopa extended-release tablets should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of carbidopa and levodopa extended-release tablets 50 mg/200 mg b.i.d.
Patients not receiving levodopa:
In patients with mild to moderate disease, the initial recommended dose is 1 tablet of carbidopa and levodopa extended-release tablets 50 mg/200 mg b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration with Carbidopa and Levodopa Extended-Release Tablets

Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with doses of carbidopa and levodopa extended-release tablets that provide 400 to 1,600 mg of levodopa per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses of carbidopa and levodopa extended-release tablets (2,400 mg or more of levodopa per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.
When doses of carbidopa and levodopa extended-release tablets are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.
An interval of at least 3 days between dosage adjustments is recommended.

Maintenance

Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of carbidopa and levodopa extended-release tablets may be required.

Addition of Other Antiparkinson Medications

Anticholinergic agents, dopamine agonists, and amantadine can be given with carbidopa and levodopa extended-release tablets. Dosage adjustment of carbidopa and levodopa extended-release tablets may be necessary when these agents are added.

A dose of carbidopa and levodopa tablets 25 mg/100 mg or 10 mg/100 mg (one half or a whole tablet) can be added to the dosage regimen of carbidopa and levodopa extended-release tablets in selected patients with advanced disease who need additional immediate-release levodopa for a brief time during daytime hours.

Interruption of Therapy

Sporadic cases of hyperpyrexia and confusion have been associated with dose reductions and withdrawal of carbidopa and levodopa tablets or carbidopa and levodopa extended-release tablets. Patients should be observed carefully if abrupt reduction or discontinuation of carbidopa and levodopa extended-release tablets is required, especially if the patient is receiving neuroleptics. (See WARNINGS).
If general anesthesia is required, carbidopa and levodopa extended-release tablets may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the patient should be observed for symptoms resembling NMS, and the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

Carbidopa and levodopa extended-release tablets 50 mg/200 mg containing 50 mg of carbidopa and 200 mg of levodopa, are buff colored, oval, biconvex uncoated tablets debossed “457” on one side and scored on other side, with mottled appearance. They are supplied as follows:

NDC 0615-8181-39 blistercards of 30

Carbidopa and levodopa extended-release tablets 25 mg/100 mg containing 25 mg carbidopa and 100 mg of levodopa, are buff colored, oval, biconvex, uncoated tablets debossed “461” on one side and plain on other side, with mottled appearance. They are supplied as follows:

NDC 0615-8180-39 blistercards of 30

Storage
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature]. Store in a tightly closed container. Protected from light and moisture.
Dispense in a tightly closed, light-resistant container.

Manufactured by:

Sun Pharmaceutical Ind. Ltd.

Halol-Baroda Highway,

Halol-389 350, Gujarat, India.

Distributed by:

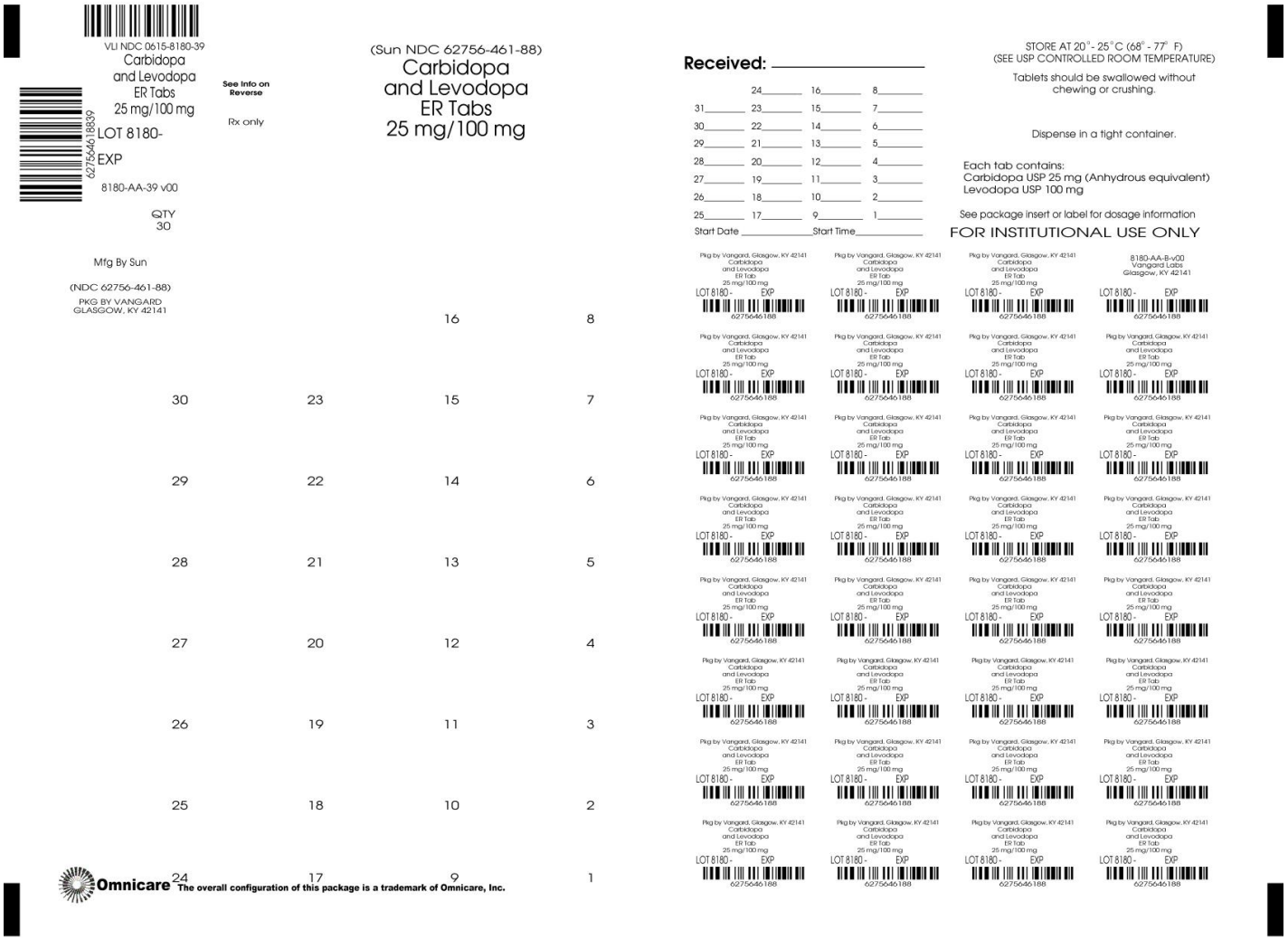
Sun Pharmaceutical Industries, Inc.

Cranbury, NJ 08512

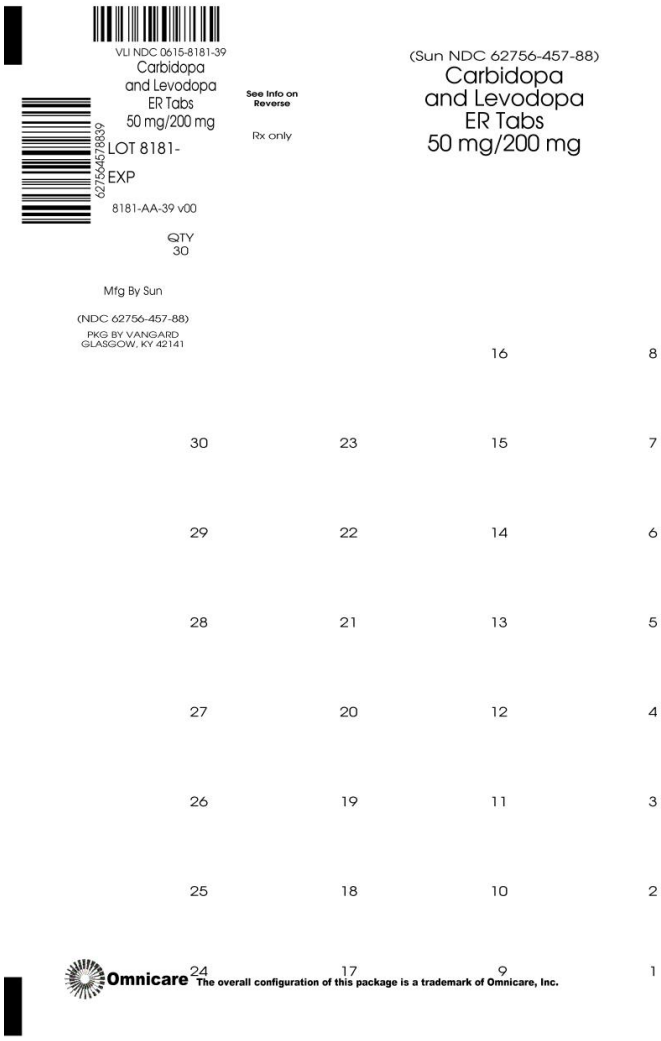
PJPI0128B

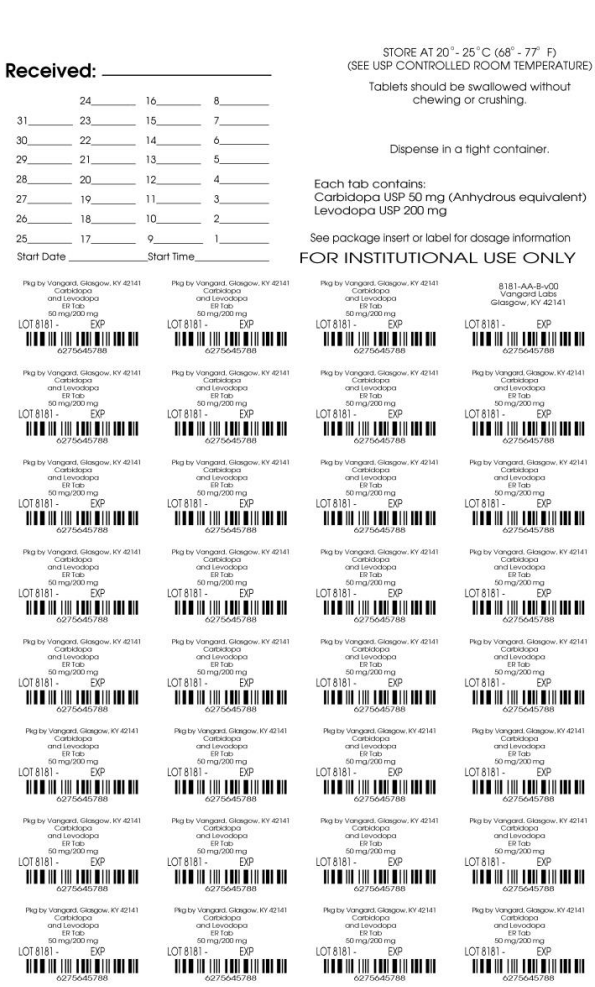
ISS. 02/2015

PRINCIPAL DISPLAY PANEL - label-25mg/100mg



PRINCIPAL DISPLAY PANEL - label-50mg/200mg





CARBIDOPA AND LEVODOPA

carbidopa and levodopa tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0615-8180(NDC:62756-461)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CARBIDOPA (UNII: MNX7R8C5VO) (CARBIDOPA ANHYDROUS - UNII:KR87B45RGH)	CARBIDOPA ANHYDROUS	25 mg
LEVODOPA (UNII: 46627O600J) (LEVODOPA - UNII:46627O600J)	LEVODOPA	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROXYPROPYL CELLULOSE (90000 WAMW) (UNII: UKE75GEA7F)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	ORANGE (buff)	**Score**	no score
Shape	OVAL	**Size**	10mm
Flavor		**Imprint Code**	461
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0615-8180-39	30 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/07/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077828	08/23/2007	

CARBIDOPA AND LEVODOPA

carbidopa and levodopa tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0615-8181(NDC:62756-457)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CARBIDOPA (UNII: MNX7R8C5VO) (CARBIDOPA ANHYDROUS - UNII:KR87B45RGH)	CARBIDOPA ANHYDROUS	50 mg
LEVODOPA (UNII: 46627O600J) (LEVODOPA - UNII:46627O600J)	LEVODOPA	200 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
HYDROXYPROPYL CELLULOSE (90000 WAMW) (UNII: UKE75GEA7F)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	ORANGE (buff)	**Score**	2 pieces
Shape	OVAL	**Size**	13mm
Flavor		**Imprint Code**	457
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0615-8181-39	30 in 1 BLISTER PACK; Type 0: Not a Combination Product	10/07/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077828	08/23/2007	

Labeler - NCS HealthCare of KY, Inc dba Vangard Labs (050052943)

Establishment

Name	Address	ID/FEI	Business Operations
NCS HealthCare of KY, Inc dba Vangard Labs		050052943	REPACK(0615-8180, 0615-8181)

Revised: 11/2020 NCS HealthCare of KY, Inc dba Vangard Labs